Acta Derm Venereol (Stockh) 1987; 67: 55–61

Antipsoriatic Activity of 10-Acyl Analogues of Dithranol (Anthralin)

II. *Clinical Comparison of Dithranol and Butantrone Sticks with Special Reference to Side Effects*

HEIKKI BRANDT

Department of Dermatology, Helsinki University Central Hospital, Helsinki, Finland

Brandt H. Antipsoriatic activity of 10-acyl analogues of dithranol (anthralin). II. Clinical comparison of dithranol and butantrone sticks with special reference to side effects. Acta Derm Venereol (Stockh) 1987; 67: 55–61.

Thirty outpatients with limited (under 15% of skin area affected), symmetrical psoriasis of the plaque type were included in an open, right-left comparison study. Paraffin-based, 3% dithranol sticks (Ditrastick®, Orion Pharmaceutica, Espoo, Finland) and similar, equimolar 4% butantrone sticks were used. Antipsoriatic activity, staining of the skin and clothes and irritation were the parameters followed up. An overall evaluation was made at the end of the trial. The antipsoriatic activity of dithranol and butantrone was almost equal at equimolar concentations. Staining of the skin was significantly (at least $p<0.05$) milder with butantrone after 2 to 10 weeks treatment. Staining of clothes was less on the butantrone side for up to three months of use but was thereafter similar to that of dithranol. Irritation caused by butantrone reached its maximum only after 6 to 10 weeks and remained on average below the level of initial dithranol irritation. Six patients discontinued the treatment due to irritation by both preparations. Four patients tolerated better dithranol than butantrone. One patient could not use dithranol but cleared with butantrone. Thus, even if butantrone has an antipsoriatic efficacy almost equal to that of dithranol and is less staining than dithranol, it causes in some patients slowly increasing irritation with Koebner-like deterioration of the disease after some weeks of uneventful overnight use. *Key Words: Psoriasis; Stick treatment; Irritation; Staining.* (Received June 6, 1986.)

H. Brandt, Mechelininkatu 25 A 11, SF-00100 Helsinki, Finland.

Dithranol (anthralin) has been one of the mainstays of topical treatment of psoriasis for 70 years and is still one of the most effective antipsoriatic drugs (1, 2). Dithranol has mostly been used in paste formulations which are messy and unsuitable for application at home. The common side effects, irritation and staining of the skin and clothing, have restricted its use mainly to hospitals. Increasing costs of hospital care has made it necessary to look for other alternatives and to develop ambulatory treatment regimens usable at home and day care treatment centers (3). Dithranol cream (4, 5) and stick (6, 7) formulations serve that purpose, making this antipsoriatic drug better acceptable for treatment at home. The Finnish dithranol stick, Ditrastick®, is based on a mixture of three paraffins, a formulation in which dithranol is stable without any antioxidants (8). However, even in this stick formulation the side effects of dithranol still persist, although milder than with conventional dithranol pastes (7).

In order to minimize the side effects of dithranol, some analogues have been developed. One of these 10-acyl analogues, 10-butyryl dithranol or butantrone, was chosen for further studies. In clinico-pharmacological and Phase I studies it has been shown to have an antipsoriatic activity about equal to that of dithranol in equimolar concentrations, and to cause less irritation and staining of the healthy skin (9, 10, 11). The aim of this study was thus to compare dithranol and butantrone in equimolar concentrations in paraffin-based sticks in the ambulatory treatment of psoriasis.

PATIENTS AND METHODS

Thirty psoriasis patients, 15 males and 15 females, 13 to 76 years of age (mean age 39 years), were included in the study. The patients had psoriasis of the plaque type, which was quite symmetrical and relatively limited. In 22 out of 30 patients the area affected was 1–5% of the total skin area. Five patients had 6–10% and three patients 11–15% of the skin area involved. Patients with pustular or exudative psoriasis or widespread disease requiring systemic or PUVA treatment were excluded, as were also pregnant women. The disease had persisted for 0.5–34 years (mean 10 years). The treatment was given at the outpatient clinic of the Department of Dermatology, Helsinki University Central Hospital. Informed consent was obtained, and the trial design was accepted by the Ethical Committee of the hospital.

The trial followed an open design. The psoriatic plaques on the right side of the body were treated with 3% dithranol sticks (Ditrastick®, Orion Pharmaceutica, Finland) and those on the left side with 4% butantrone sticks (Orion Pharmaceutica, Finland). Each patient thus acted as his/her own control. The patients were advised to use the sticks once daily in the evening and to take a shower the next morning. They were instructed to apply the stick preparation only on the plaques and to avoid application on the healthy skin. In case of irritation on either side a 1–3-day pause and use of emollients were recommended. The treatment was then continued as before until clearing of the lesions, and in case of partial or absent response for up to 24 weeks. No concomitant antipsoriatic medication was used on the areas treated with the stick preparations. The face, scalp, flexures, palms and soles were not treated with the stick preparations. The antipsoriatic efficacy of the medication and side effects were evaluated on assessment visits first after two weeks and then at four-week intervals.

The thickness of the plaques was recorded by palpation using a four-step score (3–0); thick, medium, thin, not palpable. Irritation and staining of the surrounding skin were also recorded by a four-step score (0–3); none, slight, medium, severe. Staining of the clothes was defined as none, slight, disturbig (0–2). At the end of the trial, an overall evaluation was made using the following scale; good (lesions cleared totally or nearly to tally), moderate (lesions thinned and softened) or poor (unsatisfactory result, treatment discontinued due to side effects and/or absent response). All evaluations were made by the author.

Some of the patients with irritation due to butantrone were tested for allergy using the Finn-Chamber® technique (12). The patients with complete clearing on both sides were asked to contact the outpatient department after possible relapse in order to evaluate the remission time.

Statistics

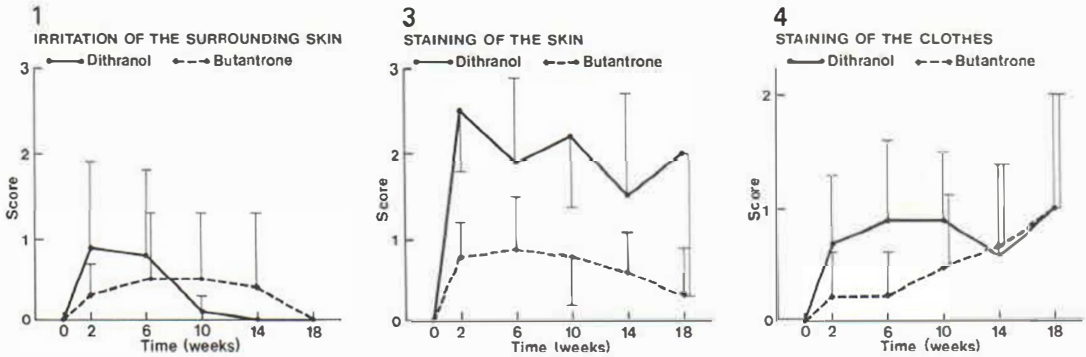
The statistical evaluation between dithranol and butantrone in terms of efficacy, irritation and staining of the skin and clothes was made after two, six and ten weeks treatment using Wilcoxon's matched pairs signed-rank test. A two sided probability $p<0.05$ was considered statistically significant. McNemar's χ^2 test was applied to overall evaluation.

RESULTS

There was no significant difference in the antipsoriatic efficacy, i.e. in the thickness scores of the plaques, between the right side treated with dithranol and the left side treated with butantrone (Table I). Complete clearing of the plaques on both sides was achieved in 8 patients (27%). Furthermore, a good antipsoriatic effect (final score ≤ 1) on both sides was recorded in 10 patients (33%). One patient had partial clearing of plaques on both sides. The treatment time of these patients ranged from 4 to 40 weeks with a median of three months.

The trial was discontinued because of irritation around the treated area in 10 patients (33%) on the butantrone side and in 7 patients (23%) on the dithranol side. The treatment time in this group ranged from 3 to 27 weeks with a median of 2.5 months. Of the 10 patients discontinuing butantrone, 6 could not even tolerate dithranol. In these 6 patients there was also a poor antipsoriatic response due to treatment pauses. In 4 cases dithranol treatment was continued with good results, although butantrone was too irritative. However, one patient hyperreactive to dithranol cleared completely with butantrone.

Irritation of the skin surrounding the plaques treated with butantrone differed from that around the dithranol-treated lesions. All patients reported irritation and treatment pauses



Figs 1, 3, 4. Course of the side effects of dithranol and butantrone during 18 weeks of treatment.

on the dithranol side already after the first few applications, while irritation on the butantrone side developed gradually, being most prominent only after 6 to 10 weeks treatment (Fig. 1). The difference between the treatments was statistically significant after two weeks treatment ($p<0.01$). In some cases a more widespread Koebner-like deterioration of psoriasis accompanied the delayed butantrone irritation (Fig. 2).

Five of the 10 patients with irritation due to butantrone were tested for possible allergy to the medications. All tested patients exhibited toxic erythema reactions to 0.01% dithranol in petrolatum after 24 hours exposure, but none reacted to an equimolar 0.015% butantrone concentration. None showed eczematous allergic reactions during the 7-day observation of the test sites.

Staining of the skin was statistically significantly milder ($p<0.001$ after 2 and 6 weeks treatment and $p<0.05$ after 10 weeks treatment) on the butantrone side (Fig. 3). Staining of clothes was most marked with dithranol during the first three months, but thereafter also butantrone caused staining (Fig. 4.). The difference in staining of the clothes between the treatments was statistically significant after 6 weeks treatment ($p<0.01$).

According to overall evaluation of the 30 patients included in the study, 20 had a favourable result, i.e. cleared or improved, with butantrone and 23 with dithranol (Table II). The result was evaluated as poor in 7 patients on the dithranol side and in 10 patients on the butantrone side, i.e. the treatment was discontinued. Six of these patients exhibited absent response with both medications.

Table I. *Antipsoriatic efficacy (thinning of lesions)*

D = dithranol side, B = butantrone side. Treatment time: mean 12.5±8.7 weeks, range 3-40 weeks

	Before $N=30$		After $N=30$	
Score	D	B	D	B
3 thick	7	7	1	1
2 medium	12	12	5	5
1 thin	11	11	14	15
0 not palpable	–	–	10	9
Score $\bar{X}\pm SD$	1.9±0.8	1.9±0.8	0.7±0.8***	0.8±0.8***

*** $p<0.001$ compared to pretreatment scores.

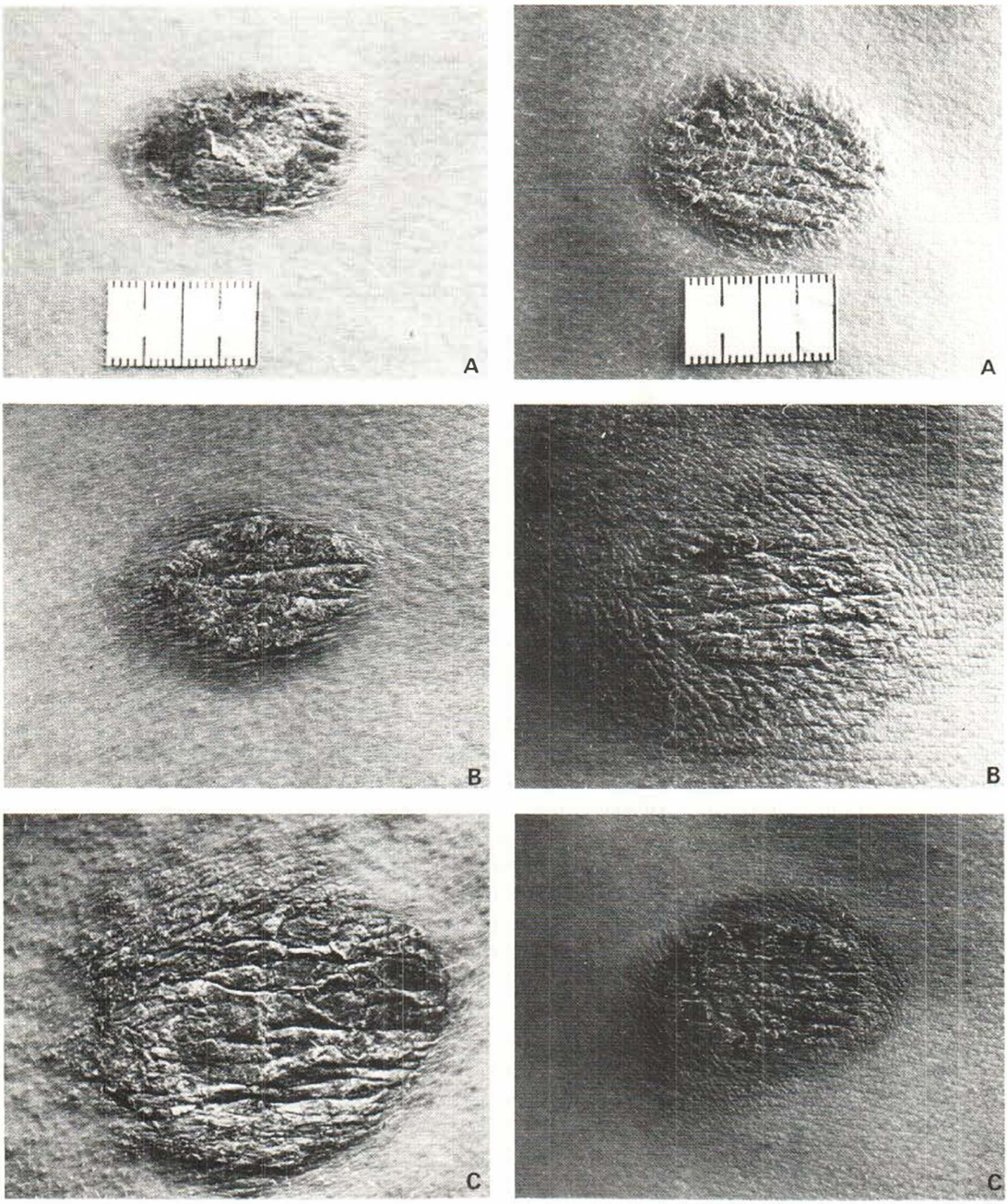


Fig. 2. (A) An 18-year-old man with symmetrical psoriatic lesions on both sides of the chest. (B) After four weeks of treatment. Irritation and staining around the lesion treated with dithranol (right). No irritation on the butantrone side. Some staining on a narrow rim around the lesion (left). (C) After eight weeks of treatment. No more irritation on the dithranol side. Reddish brown staining around the plaque (right). Koebner-like deterioration and follicular irritation on the butantrone side, only slight staining. Treatment descontinued due to butantrone irritation and absent response to both medications.

Table II. *Overall evaluation*

Good = lesions cleared totally/nearly totally, Moderate = lesions thinned and softened, Poor = unsatisfactory result, treatment discontinued due to side effects and/or absent response

	Treatment	
Evaluation	Dithranol *N*	Butantrone[a] *N*
Good	22	19
Moderate	1	1
Poor	7	10

[a] McNemar test $\chi^2=0.80$, non significant.

Eight patients with complete or nearly total clearing with both drugs attended follow-up visits during 12 months after completing the trial. The mean remission time was 4.4 months (range 0.3–12 months) on both drugs.

DISCUSSION

In this study, as in the Phase I clinical trial on butantrone (10), the antipsoriatic efficacy of butantrone did not significantly differ from that of dithranol in equimolar concentrations. In 63% butantrone and in 73% dithranol gave a good therapeutic result. This is in accordance with the previous study on Ditrastick (7), in which about 70% of patients achieved an excellent or good result.

In long-term use the 3% dithranol stick was generally better tolerated than the equimolar 4% butantrone stick despite the common initial irritation by dithranol. All patients in this study reported irritation of the skin surrounding the plaques treated with 3% Ditrastick after the first few applications. The irritation disappeared after an interval of 1–3 days during which time emollients only were used. This initial irritation by dithranol did not cause discontinuation of the treatment. Because of repeated irritations dithranol had to be discontinued in 23% of patients. In the previous study on Ditrastick (7), about 21% of patients discontinued the treatment because of inefficacy or side effects.

On the butantrone side there was no initial irritation. The intensity of the irritation increased gradually reaching its maximum after 6 to 10 weeks treatment. This reaction, with Koebner-like deterioration around the treated areas in some patients, was more difficult to manage than the dithranol irritation, leading to discontinuation of the treatment. In this study the median treatment time to reach favourable results was 12 weeks. The time of maximal butantrone irritation is rather close to this point. this means that an initially good result of the treatment may unexpectedly be reversed, disappointing both the patient and the physician. The slowly increasing irritiation by butantrone, which caused discontinuation of the treatment in about one-third of the patients, could be due to cumulation of the more slowly oxidizable 10-acyl derivative (cf. 13).

The cumulative butantrone irritation was even more clearly seen in an open multicenter trial on 4% butantrone stick used in an overnight regimen (unpublished data). In that study 141 patients suffering from mild or moderate plaque type psoriasis were treated for 7.7 weeks in mean. Calming down of symptoms of irritation and restart of treatment were not allowed. thus an apparent reaction of irritation of any degree, mostly after 4 to 8 weeks' treatment, caused discontinuation. In 90 patients (63%) there was such delayed irritation and in 39 patients (28%) it was severe, six of these patients being even hospitalized for

some days. Two of them had fever and transient leukocytosis, but no other signs of systemic effects were recognized. About half of the patients (48%) in this multicenter study reacted favourable to the overnight treatment with butantrone sticks.

The present study showed no evidence of allergy either to dithranol or butantrone. In the literature, there are only few case reports of possible allergy to dithranol (14, 15, 16) despite the widespread use of this drug for 70 years.

Butantrone caused significantly less staining of the skin and during the first months of treatment also less staining of the clothes than dithranol. This is a remarkable advantage in outpatient practice. The gradually increasing staining of clothes may be due to slow splitting of the 10-acyl chain and oxidation both to anthraquinone and to polymers in the alkaline milieau when repeatedly washing the clothes.

The remission time of the patients, who cleared symmetrically with both medications, was about 4.5 months. This is in accordance with other experiences of the long-lasting remission after dithranol treatment. Seville (17) has reported of a mean remission time of seven months with dithranol.

Some of the problems related to dithranol treatment, especially staining of skin and clothes, have partially been obviated by using short contact or minutes therepy (18, 19) in which the surplus of dithranol is removed within one hour or less. There is evidence (20) that the short contact modality would prevent cumulation and late irritation due to the overnight treatment with butantrone.

REFERENCES

1. Rogers S, Marks J, Shuster S, Vella Briffa D, Warin A, Greaves M. Comparison of photochemotherapy and dithranol in the treatment of chronic plaque psoriasis. Lancet 1979; i: 455–458.
2. Gorsulowsky DC, Ellis CN, Voorhees JJ. Anthralin in psoriasis therapy. Seminars in dermatology. New York, Thieme Inc., 1985; vol. 4, 4: 321–324.
3. Farber EM, Nall L. Psoriasis, a review of recent advances in treatment. Drugs 1984; 28: 324–346.
4. Larkö O. En ny ditranolkräm jämförd med placebo och UVB vid behandling av psoriasis. Läkartidningen 1983; 80: 1788–1790.
5. Gip L, Zador G. Treatment of psoriasis with dithranol cream 0.1% and 0.25% in comparison with dithranol ointment 0.1% and 0.25%. Curr Ther Res 1984; 36: 421–425.
6. Chalmers RJG, Marks J, Shuster S. A novel wax stick preparation of anthralin. Acta Derm Venereol (Stockh) 1982; 62: 181–182.
7. Brandt H, Gordin A, Mustakallio KK. Ambulatory treatment of psoriasis with dithranol sticks—a novel paraffin formulation. Dermatologica 1985; 171: 459–462.
8. Mustakallio KK, Brandt H. New formulations of dithranol (anthralin) for ambulatory treatment of psoriasis. Acta Pharm Suecica 1983; 20: 44–45.
9. Brandt H, Mustakallio KK. Irritation and staining by dithranol (anthralin) and related compounds. III. Cumulative irritancy and staining during repeated chamber testing. Acta Derm Venereol (Stockh) 1983; 63: 237–240.
10. Mustakallio KK, Brandt H. Antipsoriatic activity of 10-acyl analogues of dithranol (anthralin). I. Phase I clinical trial of 10-propionyl dithranol and 10-butyryldithranol (butantrone). Acta Derm Venereol (Stockh) 1984; 64: 63–66.
11. Mustakallio KK, Brandt H, Halmekoski J, Männistö PT. Butantrone, a less toxic and less staining substitute for dithranol (anthralin). Acta Derm Venereol (Stockh) 1984; 64, Suppl 113: 156–157.
12. Pirilä, V. Chamber test versus patch test for epicutaneous testing. Contact Dermatitis 1975; 1: 48–52.
13. Taskinen J, Haarala J, Wartiovaara E, Halmekoski J. ●xidation of antipsoriatic 10-acyldithranol derivatives to 1, 8-dihydroxyanthraquinone. In: FIP-85 Abstracts. 45th International Congress of Pharmaceutical Sciences, Montreal, 1985: 255.
14. de Groot AC, Nater JP. Contact allergy to dithranol. Contact Dermatitis 1981; 7: 5–8.
15. Lawlor F, Hudson C. Allergy to dithranol. Contact Dermatitis 1982; 8: 137–138.
16. Schauder S. Allergische Kontaktekzem auf Cignolin® (Dithranol). Z Hautkr 1984; 59: 773–774.

17. Seville RH. Relapse rate of psoriasis worsened by adding steroids to a dithranol regime. Br J Dermatol 1965; 95: 643–646.
18. Schaefer H, Farber EM, Goldberg L, Schalla W. Limited application period for dithranol in psoriasis. Br J Dermatol 1980; 102: 571–573.
19. Runne U, Kunze J. Die Minutentherapie der Psoriasis mit Dithranol und ihre Modifikationen. Eine kritische Wertung anhand von 315 Patienten. Hautarzt 1985; 36: 40–46.
20. Göransson A. Irritation and staining by dithranol (anthralin) and butantrone (10-butyryl dithranol). Further short contact and tape stripping experiments. Acta Derm Venereol (in press, 1986).